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(54)【発明の名称】　ミクロスポリディア症の治療におけるベンゾイミダゾール駆虫薬の使用

(57)【要約】
ミクロポリディア症の治療におけるベンゾイミダゾール駆虫薬の使用。

請求の範囲

1．ミクロスポリディア症の治療用薬物の製造用ベンゾイミダゾール駆虫薬。

2．ベンゾイミダゾール駆虫薬がアルベンダゾールである請求項1記載の使用。

3．処置される患者がヒト免疫不全ウイルス（ＨＩＶ）にも感染している請求項2記載の使用。

4．ミクロスポリディア症が下痢の原因となる感染である請求項3記載の使用。

明　細　書

ミクロスポリディア症の治療におけるベンゾイミダゾール駆虫薬の使用

本発明は、ミクロスポリディアによって引き起こされる疾患の治療、特に、ヒト免疫不全ウイルス（ＨＩＶ）に感染している患者の下痢の治療における、ある種のベンゾイミダゾール化合物の使用に関する。

動物が感染するプロトゾア・ミクロスポリディア（protozoa microsporidia）は５００種類を超える。急性免疫不全症候群（ＡＩＤＳ）の出現までは、ヒト感染は珍しく、1、2件の報告および症例に限られていた。しかしながら、現在、ミクロスポリディア症は、ＨＩＶ感染個体の小腸において共通しており、下痢の原因と考えられる。アメリカ合衆国における最近の研究では、下痢の原因として他の病原体が確認されていない患者の3分の1は、空腸生検材中にミクロスポリディア胃感染を持つことが判明した［ヒューマン・パッソロジー（Human Pathology）、１９９０、２１（５）、４７５－８２］。最近、英国の研究では、非常に類似の形態が得られた［ピーコック（Peacock）ら、ジャーナル・オブ・クリニカル・パッソロジー（J. Clin. Path.）１９９１、印刷中］。しかしながら、ミクロスポリディア病が下痢の原因において病原体的重要性を有するものであるという顕著な証拠は、好適な化学的治療剤でこの微生物を全滅させる能力、または、別法として、好適な動物モデルの開発を必要とする。かかる好適な化学的治療剤は、現在でも、入手可能ではない。

本発明は、この要求を満足するものであり、第１の態様において、ヒト免疫不全ウイルス（ＨＩＶ）に感染している患者における、ミクロスポリディア症の治療用、特に、例えば、下痢の原因となるミクロスポリディア症のようなミクロスポリディア症の治療用薬物の製造において使用するためのベンゾイミダゾール駆虫薬アルベンダゾールを提供するものである。

より広範囲の態様において、本発明は、ヒト免疫不全ウイルス（ＨＩＶ）に感染している患者における、ミクロスポリディア症の治療用、特に、下痢の原因となるミクロスポリディア症のようなミクロスポリディア症の治療用薬物の製造において使用するためのベンゾイミダゾール駆虫薬を提供するものである。

「ベンゾイミダゾール駆虫薬」なる語は、広域駆虫薬として作用することが知られているいずれのベンゾイミダゾール含有薬物をも含むことを意図する。例えば、かかる化合物としては、アルベンダゾールに加えて、フェンベンダゾール、オキシベンダゾール、メベンダゾールおよびパルベンダゾールが挙げられる。

さらなる態様では、本発明は、ミクロスポリディア症の治療が必要な対象に、例えばアルベンダゾールのようなベンゾイミダゾール駆虫薬の有効量を投与することからなる、ミクロスポリディア症の治療方法を提供する。特に、本発明は、ヒト免疫不全ウイルス（ＨＩＶ）に感染している患者において、ミクロスポリディア症、例えば、下痢の原因となるミクロスポリディア症の治療方法を提供する。

本発明で使用する場合、活性剤は、標準的な医薬組成物、例えば錠剤組成物に調剤化される。

活性剤の好適な用量は、1日当たり１００～５０００mgの範囲であり、該化合物は、症状を処置し、かつ、患者の感染からの解放を維持することが必要である限りは、1個以上の離散性投与単位で、1日1回または2回、投与される。用量計画法のサイズ、回数および期間は、もちろん、感染の重篤度に左右されるであろう。

結果

下痢を有し、空腸生検でミクロスポリディア症を示した6体のＨＩＶ感染個体で研究を行った。

該患者をアルベンダゾール（４００mg、b. i. d.）で、1週間以内で処置し、6体のうち5体は、下痢が完全になくなるという劇的な症候性改善があり、体重低下が阻止された。結果として、2体の患者は、非下痢性の原因で死亡し、1カ月の治療を完了した残りの4体のうち2体は再発した。

これらの患者のうちの5体において治療の後に行った空腸生検によって、ミクロスポリディア胃の栄養の脱落が示されるが、明らかな成熟は阻止され、その結果、感染なメロント期が見られるが、成熟胞子はない。

国際調査報告

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I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)

According to International Patent Classification (IPC) or to both National Classification and IPC

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II. FIELDS SEARCHED

Minimum Documentation Searched

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched

III. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	FR,A, 4761 (CRIMETRON) 20 February 1967, see page 1, left-hand column, lines 1-15	1
P,X	AIDS Care, volume 3, no. 4, 19 December 1991, E.K. Gaydos: "Current treatment of opportunistic infections in HIV disease", pages 461-466, see page 464	1-4
P,X	STN Information Service, file BIOSIS, abstract number 91:448880, "Treatment of intestinal "microsporidiosis" with albendazole". VII International Conference on AIDS: Science Challenging Aids; Florence, IT, June 16-21, 1991. 4649, (vol. 1); 4609. (vol. 2), see the whole spection	1-4

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,X	J. Protozool, volume 38, no. 6, 1991, Society of Protozoologists, 1991; E.U. Canning et al.: "In vitro and in vivo investigations of human microsporidia", pages 631-635, see page 634	1,2

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国際調査報告

GB 9200522
SA 57702

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A- 4761		None	

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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(54) Title: USE OF BENZIMIDAZOLE ANTHELMINTIC IN THE TREATMENT OF MICROSPORIDIAL INFECTIONS

(57) Abstract

The use of a benzimidazole anthelmintic in the treatment of microsporidial infection.

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USE OF A BENZIMIDAZOLE ANTHELMINTIC IN THE TREATMENT OF MICROSPORIDIAL INFECTIONS

The present invention relates to the use of certain benzimidazole compounds in the treatment of diseases caused by microsporidia organisms, in particular the treatment of diarrhoea in patients infected with human immunodeficiency virus (HIV).

There are more than 500 species of the protozoa microsporidia which infect animals. Until the advent of acquired immune deficiency syndrome (AIDS) human infection was rare and confined to one or two cases of encephalitis and myositis. Now, however, microsporidium infection is common in the small intestine of HIV infected individuals and is thought to cause diarrhoea. In a recent study in the USA a third of patients in whom no other pathogen as a cause of diarrhoea had been uncovered, were found to have microsporidiosis infection in jejunal biopsy material (Human Pathology, 1990, 21(5), 475-81). Very similar figures were recently obtained in a UK study (Peacock et al., J. Clin. Path. 1991, in press). However, positive proof that Microsporidiosis is of pathogenic importance in the development of diarrhoea requires the ability to eradicate this organism with suitable chemotherapeutic agents or, alternatively, the development of suitable animal models. Such suitable chemotherapeutic agents have, until now, not been available.

The present invention fulfils this need and provides in a first aspect, the benzimidazole anthelmintic albendazole, for use in the manufacture of a medicament for use in the treatment of microsporidia infections, in particular in the treatment of microsporidia infection, for example diarrhoea-causing microsporidial infection, in patients infected with the human immunodeficiency virus (HIV).

In a broader aspect, the invention provides a benzimidazole anthelmintic for use in the manufacture of a medicament for use in the treatment of microsporidia infections, in particular in the treatment of microsporidia infection, for example diarrhoea-causing microsporidia infection, in patients infected with the human immunodeficiency virus (HIV).

The term 'benzimidazole anthelmintic' is intended to include any benzimidazole containing agent which is known to act as a broad spectrum anthelmintic. For example, in addition to albendazole, such compounds include fenbendazole, oxibendazole, mebendazole and parbendazole.

In a further aspect the present invention provides a method of treatment of microsporidial infection which comprises administration to a subject in need thereof of an effective amount of a benzimidazole anthelmintic, for example albendazole. In particular the invention provides a method for the treatment of microsporidial infection, for example diarrhoea-causing microsporidial infection, in patients infected with the human immunodeficiency virus (HIV).

When used in the present invention, the active agent is formulated in a standard pharmaceutical composition, for example in a tablet composition.

Suitable doses of active agent will be in the range of from 100 to 5000mg per day, the compound being administered in one or more discrete dosage units, once or twice a day, for as long as is necessary to treat the condition and maintain the patient free of infection. The size, frequency and duration of the dosage regimen will, of course, depend on the severity of the infection.

RESULTS

A study was carried out on 6 HIV infected individuals with diarrhoea and proven microsporidial infection on jejunal biopsy.

The patients were treated with albendazole (400mg, b.i.d.) and within 1 week, 5 of the 6 had had dramatic symptomatic improvement with complete loss of diarrhoea and arrested weight loss. Subsequently, two patients died of non-diarrhoeal causes and of the remaining 4 who completed one month's treatment, two relapsed.

Jejunal biopsies performed following therapy in five of these patients have shown continuing evidence of Microsporidiosis but an apparent maturation arrest so that frequent meronts are seen but mature spores are not.

CLAIMS:

1. A benzimidazole anthelmintic for use in the manufacture of a medicament for use in the treatment of microsporidial infection.

2. The use according to claim 1 in which the benzimidazole anthelmintic is albendazole.

3. The use according to claim 2 in which the patient treated is also infected with human immunodeficiency virus (HIV).

4. The use according to claim 3 in which the microsporidial infection is a diarrhoea-causing infection.

INTERNATIONAL SEARCH REPORT

International Application PCT/GB 92/00522

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

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Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

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